UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT:	Review of the Sinanen Co., Limited Zeomic® Type AJ Silver Zeolite A for Risk Assessment to Add Certain Uses to the Product Label
TO:	Marshall Swindell, Product Manager Team 33 Regulatory Management Branch II Antimicrobials Division(7509C)
FROM:	Robert Quick, Chemist Robert Quick Risk Assessment and Science Support Branch Antimicrobials Division(7509C)
THRU:	Norm Cook, Chief Norman P. Cook 12.11.01 Risk Assessment and Science Support Branch Antimicrobials Division(7509C)
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Introduction:

Technology Sciences Group, Inc.on behalf of the Sinanen Company, Ltd. has submitted a registration request for a name change of the existing product, Zeomic® Type AJ10D Silver Zeolite A, to the new primary name of, Zeomic® Type AJ Silver Zeolite A. This product is for the use of the active ingredient, silver for use in various articles. The materials into which the product will be incorporated include plastics, rubber, paper, fibers, etc. The registered product permits use in materials that will be used for both food and non-food contact uses.The revised label includes newly proposed uses on additional items including garbage bags and garbage cans; office equipment; toys; spas, bathtubs, showers, and filters and components thereof; personal care items(including grooming items, toothbrushes, cosmetic brushes and mouthguards); diapers; and HVAC and HVAC related materials. Items which would involve oral, but not dietary, exposure in this expanded usage include toys, tooth brushes and mouthguards for which there will be oral exposure. The label is structured to show the types of finished products into which the product can be incorporated: Plastics-including films, sheets, slabs and molded plastic parts; Fibers; Coatings, Films and Laminates; Adhesives and Sealants; and other Miscellaneous Applications.

The revised label which includes the new uses and which includes uses for toys, toothbrushes and mouthguards is structured to include toys, toothbrushes and mouthguards under the "Plastics" section of the label and includes toothbrushes under the "Fibers" section of the label. Note: It is conceiveable that toys could also be included under the "Fibers" section.

There are two submissions. The first submission dated December 8, 2000, includes a letter from Technology Sciences Group Inc., the revised labelling which includes the product name change and the new use sites, the Confidential Statement of Formula and a report entitled *Evaluation of the Potential Health Risks Associated with Zeomic® Type AJ10D Silver Zeolite A* authored by Gary Burin and David Brookman dated November 9, 2000, MRID# 452917-01. The second submission dated June 29, 2001, includes responses to the analytical method questions raised in our earlier AD May 30, 2000, memo for the previous Sinanen submission involving water contact articles.

This memo will address the question of whether the migration study previously evaluated and entitled, "Migration Studies And Extraction Data From LDPE Films Containing Zeomic® Silver Zeolite A", can be used to evaluate the residential exposure that will result from the toys, toothbrushes and mouthguards uses proposed with this registration, the oral exposure from these new uses and the analytical method questions raised in an earlier RASSB review of the water contact article submission. This memo will not discuss the oral exposure for uses which are already registered on the label.

Background:

There are no tolerances or tolerance exemptions established under 40 CFR 180 for silver or silver nitrate.

The Zeomic® Type AJ10D Silver Zeolite product is registered for many uses including a water contact use.

The product, Zeomic® Type AJ10D Silver Zeolite, is listed in REFS as approved on 05/13/99 and with a label approval date of 02/01.

Note: The "bean sheets" for these actions list the active ingredient as silver nitrate with a PC code of 072503. The EPA REFS site shows this product under "silver" with a PC code of 072501.

Conclusions:

1. The questions raised in the RASSB review dated May 30, 2000 for water contact articles, by Robert Quick which related to the analytical method used for analysis in the migration study have been resolved. The method is adequate to determine residues of silver in the migration study that was submitted in the previous registration action for this product for water contact articles.

2. This review assumes that the residue of concern that result from the use of this product is silver. Other residues that could be extracted from the Zeomic® material are [redacted] and [redacted].

3. RASSB concludes that the previously submitted and reviewed migration study for water contact articles is translatable to the articles proposed for impregnation in this registration - mouthguards, toothbrushes and toys - which will have saliva contact.

4. Based on the water contact migration study, RASSB has calculated the following levels of silver oral ingestion for the mouthguard, toothbrush and toy uses proposed in this registration:

a) For mouthguards: 0.54 µg Ag/day or 0.009 µg Ag/kg bw/day for a 60 kg adult.
b) For toothbrushes: 1.7×10^{-3} µg Ag/day or 2.8×10^{-5} µg Ag/kg bw/day for a 60 kg adult and 1.1×10^{-4} µg Ag/kg bw for a 15 kg child.
c) For toys: 4.3 µg Ag/day or 0.29 µg Ag/kg bw/day for a 2-5 year old 15 kg child.

Recommendations:

RASSB has no residue chemistry objections to the granting of this requested registration.

Detailed Considerations

OPPTS GLN 860.1100 Chemical Identity

The name of the product that is to be incorporated into the plastics, fibers, coatings, films, laminates, adhesives, sealants, etc. materials is Zeomic® Type AJ Silver Zeolite A. The label has an ingredient statement claim of 2.5% silver. The product label states that the Zeomic® additive can be incorporated into finished plastic products, fibers, coatings, films, laminates, adhesives,

sealants and in miscellaneous applications at up to 5.0% by weight. The intended use of the antimicrobial is to protect the treated article. The label states that "When incorporated into treated articles, this product does not protect users of any such treated article or others against food borne or disease causing bacteria, viruses, germs, or other disease causing organisms".

Component(CAS #)	Empirical Formula	Formula Weight
Silver nitrate (CAS # 7761-88-8)	$AgNO_3$	169.9

OPPTS GLN 860.1200 Proposed Use

The product, Zeomic® Type AJ Silver Zeolite A, is to be used as an additive incorporated into or as a coating on a large variety of plastics, fibers, coatings, films, laminates, adhesives, sealants, etc. The existing label lists a large number of both food and nonfood contact uses.

The uses that are to be added to the label are for garbage cans and garbage bags; office equipment; drain pan liners; spas, bathtubs, showers and filters and components thereof; personal care items(including grooming items, tooth brushes, mouthguards); toys; diapers; HVAC and related items(including insulation, ducts, heat exchangers, drain pans, air filters, air purifiers, diffusers, and parts and components thereof).

The new additions to the label do not include any food contact uses. The new uses for toys, toothbrushes and mouth guards do include oral exposure in addition to dermal exposure.

OPPTS GLN 860.1300 Nature of the Residue

No information is provided as to the nature of the residue that will leach from the treated article. The likely residue of concern that will migrate to the surface of the treated article and be available for dermal or oral exposure is silver. [redacted] as well as the inert ingredients in the product may also leach from the treated article.

The label includes the following statement for all uses on the label, " Do not incorporate this product into any food contact polymer unless the subject food polymer is approved and listed in 21 CFR, Parts 174 through 186 (inclusive), or in the United States Food and Drug Administration's "Food Contact Substance Notification System". Therefore, oral exposure to the polymers permitted for use by the label directions should not have any significant toxicological concern for the non-dietary uses proposed in this revised registration.

OPPTS GLN 860.1340 Analytical Method
OPPTS GLN 860.1500 Residue Chemistry

The results of a migration study and the accompanying analytical method used in that study were

reviewed by an EPA contractor and underwent secondary review by an EPA /AD/RASSB review chemist. The study is entitled, Migration Studies and Extraction Data From LDPE Films Containing Zeomic® Silver ZeoliteA". (Note: LDPE = Low Density Polyethylene) The contractor concluded, and RASSB concurs, that the study adequately describes the migration of silver, [redacted] from the LDPE articles containing Zeomic® at a maximum concentration of 5% to food-simulating solvents. The study closely follows Food & Drug Administration(FDA) guidelines. At the time of the previous review, RASSB requested, but never received, additional information for the migration study. These were:

1. The method of sample preparation.
2. Calibration curves for silver.
3. Information on how the LOD for silver was determined(Note: LOD = Limit of Detection).

The maximum amount of silver that was extracted/leached from the LDPE articles containing Zeomic® with a label claim of 2.5% silver and at the highest label-permitted incorporation rate of 5% in the treated polymer(the label claim is presently 2.5% silver) is 30 ppb(parts per billion).

The registrant has responded to these questions with the submission dated June 29, 2001 for the new uses proposed in this registration action. The registrant's response and our AD comments to the questions follow.

1. AD question: Information on the sample preparation procedure used for silver.

The registrant response:
a) The silver caibrants were prepared by dilution of portions of commercially obtained standard solutions to the appropriate volumes in dilute nitric acid. Calibrant blanks were prepared similarly, except that the standard solution was omitted.
b) The test migration solutions were analyzed directly with no preparation.
c) Fortifications were made by addition of known amounts of standard solution to portions on the test solution blanks.

AD comments: The registrant has satisfactorily answered our earlier AD question.

2. AD question: Caibration curves for silver analysis.

The registrant response:
The calibration and test solutions were analyzed by flame atomic absorption spectroscopy using a silver hollow-cathode lamp as a light source. The registrant explains the principal of the method. Absorbance at the resonance wavelength follows Beer's law. A plot of absorbance against the concentration of the silver analyte produces a straight line within a certain range of concentrations. Because the deflection is proportional to the absorbance, a plot of deflection against concentration also produces a straight line.

The equations of the straight lines were determined by regression. New equations were determined each day that analyses were conducted. Example regression results and an example

calibration plot were submitted. Each calibrant and each test solution was aspirated in triplicate. The mean for each and its concentraion were used to generate the equation of the regression line. Then, the mean deflection for each test solution was substituted into the regression equation, yielding the concentration of silver in each test solution.

Example regression results and an example calibration plot are shown.

AD comments: The registrant has satisfactorily answered the question.

3. AD Question: A discussion on how the registrant determined the LOD for silver.

The registrant response: The limit of detection varied from day to day because the sensitivity of the spectrophometer and the conditions in the system varied from day to day. Overall, the approximate LOD for the entire study is 0.01 ppm.

The analysts estimated an LOD from the regression equations(discussed above). A deflection of zero was assumed and inserted into the regression equation. The intercept on the concentration axis(the abscissa) was taken as the LOD. Two examples are presented: one value showed an LOD of 0.005 ppm and a second value showed an LOD of 0.011 ppm. The analyst used 0.01 ppm as an estimate for the entire progam.

The registrant also presents a discussion on two different methods of supplemental calculations made from the original data following methods outlined in the FDA document, Guidance for Industry, FDA Bulletin 64 "Validation of Analytical Procedures: Methodology". Using these two methods, the LOD varied from 0.002-0.015 ppm using one method and from 0.002-0.007 ppm using the second method.

AD comments: The registrant has satisfactorily answered our question.

RASSB concludes that the analytical method used in the migration study is adequate to generate residue data and that the residue data in the study are valid to calculate the ingestion of silver residues resulting from water in contact with water contact articles.

Oral Ingestion Of Silver Resulting From The Presently Proposed Uses for Mouthguards, Toothbrushes and Toys

The migration study described above was intended to support the dietary risk assessment from drinking water in contact with water contact articles and the migration study is adequate to support that use. However, the uses proposed in this registration action involve the extraction/leaching of silver residues from the Zeomic® product by saliva in the mouth. There are no migration data for saliva. The question then becomes one of whether residue data reflecting residues extracted/leached by the 8% and the 95% ethanol food-simulating solvents used in the existing migration study can be translated to residue levels expected to be extracted from the Zeomic® product by human saliva for the uses proposed in this registration action.

After consideration of the question, RASSB concludes that, while the available migration data are not reflective of what would take place in the mouth, the data can be translated because the 8% and the 95 % ethanol food-simulating solvents reflect a wide range of solvent differences; i.e., water/alcohol solubility in the 8% mixture versus fat solubility in the 95% mixture. RASSB will use the data reflecting the 8% ethanol food-simulating solvent because it more likely reflects the characteristics of saliva and because it resulted in the highest residues extracted from the impregnated plastic. RASSB will also use the 2 hour extraction data at 100°C. and the 24 hour data reflecting extraction at 100°C for 2 hours and 49°C. for 24 hours because all of these data reflect extraction that could have occurred during a 24 hour period.

Oral Ingestion Of Silver Resulting From Oral Exposure To Zeomic® Impregnated Into Mouthguards, Toothbrushes And Toys

The registrant has used an hourly migration rate of 1.1×10^{-3} µg Ag/cm^2 which appears to be based on the 24 hour sampling intervals for the 5% Zeomic® film and did not include the residue values for the 2% film because one of the extractions for the 2% film showed no detectable residues. RASSB used both the residue values for the 2% film and 5% film in its calculation of the average residue but did not include the non-detectable value. RASSB also used the values reflecting extraction at 100°C. at the 2 hour extraction period because the 24 hour data also include a 2 hour extraction at 100°C as well as extraction at 49°C. for 24 hours. The result is that the average ppm value for Ag used by RASSB is 0.0209 ppm whereas the mean residue value used by the registrant is 0.017 ppm. This corresponds to an Ag flux rate of 1.1×10^{-3} µg/cm^2 used by the registrant and an Ag flux rate of 1.3×10^{-3} µg/cm^2 used by RASSB.

Mouthguard:

RASSB has no information on the measurements of a typical mouthguard or for the time that a mouthguard will be in the mouth per day. However, RASSB has made the following assumptions.

Assume that:

A sleeping person has a mouthguard in place for 8 hours per day.
Surface area of a typical mouthguard is 52 cm^2(4 in x 2.54cm/in) x (0.5in x 2.54cm/in) x 4 surfaces).
The hourly migration rate for silver from the Zeomic® is 1.3×10^{-3} µg/cm^2(from the migration study).

Then:

Dose rate/day for silver = 1.3×10^{-3} µg Ag/cm^2/hr x 8 hours x 52 cm^2 mouthguard = 0.54 µg Ag/(8 hours)day or **0.009 µg Ag/kg bw/day for a 60 kg adult**

This calculation was performed based on the RASSB estimate on the specifications of a typical mouthguard.

Toothbrush

Assume that:

Toothbrush surface area is 16 cm^2.
The hourly migration rate for silver from the Zeomic® is 1.3 x 10^{-3}µg Ag/cm^2/hr.
Two tooth brushings per day with each a duration of 2.5 minutes(0.042 hr).

Then:

Dose rate/day for silver = 1.3 x 10^{-3} µg Ag/cm^2/hr x 0.042 hrs/brushing x 2 brushings/day x 16 cm^2 = 1.7 x 10^{-3} µg Ag/ day or **2.8 x 10^{-5} µg Ag/kg bw for a 60 kg adult and 1.1 x 10^{-4} µg Ag/kg bw for a 15 kg child**

Toy

Assume that:

Toy surface area of 500 cm^2.
A 2-5 year 15 kg child mouths a toy for 1 minute per mouthing.
There are 39 mouthings per hour(Taken from the "Overview of Issues Related to the Standard operating procedures For Residential Exposurement Assessment" dated August 5, 1999, Page 66, Table 14 for residential children ages 2-5 years, object to mouth range maximum).
Child mouths for 10 hours per day.
The hourly migration rate is 1.3 x 10^{-3} µg Ag/cm^2/hr.

Then:

Dose rate for silver = 1.3 x 10^{-3} µg Ag/cm^2/hr x 0.017 hrs/mouthing x 39 mouthings/hr x 10 hours/day x 500 cm^2 = 4.3 µg Ag/day or **0.29 µg Ag/kg bw for a 15 kg child**